REMARKS

Claim 1 has been amended to clarify that the composition has been freeze-dried from solution. This limitation is clear from Example 3. Claim 6 has been amended simply for clarity. New claim 9 is supported on page 2 of the application, middle of the second full paragraph. No new matter has been added and entry of the amendment is respectfully requested.

Applicants wish to call the attention of the Examiner to the enclosed decision of the Board of Patent Appeals and Interferences in the parent application, US 09/888,734, (Exhibit D).

Other than double-patenting, the sole basis for rejection is for obviousness over a combination of Curtis, *et al.,* U.S. 5,824,780 in view of Livesey, *et al.,* U.S. 5,364,756 and Lee, *et al.,* EP 0314095.

The claims have been amended to delete the requirement for 1-1.5 mg calcium ion per unit of Factor VIII. The teachings of the Lee document, cited for its suggestion that calcium ion be included when freeze-drying a solution of native Factor VIII, is no longer directly relevant.

Lee teaches a different approach for stabilization of plasma protein preparations that are lyophilized. Lee suggests this can be obtained by using a high ionic strength medium. (See pages 2-3, bridging paragraph.) All of Lee's compositions contain concentrated amounts of sodium chloride. As shown in the present application, in Example 1, high salt concentrations are deleterious to the stability of Factor VIII. The compositions of the present invention do not contain high amounts of salt; rather, they rely on the action of trehalose for assuring stability.

In any case, the disclosure and claims in Lee are directed to the end formulation, not the formulation used for lyophilization.

The Office combines the teachings of Lee, *et al.,* with Curtis and Livesey. As noted, Lee is not germane to the claims as amended. Respectfully, applicant believes that

1) Curtis is irrelevant because it concerns activated Factor VIII, a different protein from the native Factor VIII of the present claims and because Curtis does not teach anything even about freeze drying activated Factor VIII, and

2) Livesey is irrelevant because it concerns freeze-drying of suspensions, not solutions of biological material, and in any event, fails to teach freeze-drying in the presence of trehalose and absence of albumin for any material.

Therefore, combination of these documents with or without Lee is inapposite.

In more detail with respect to these issues, as to Curtis: Curtis concerns, to the extent it contains any description of freeze drying at all, lyophilization only of activated Factor VIII. The present claims are directed to freeze dried compositions of stabilized native Factor VIII, a different protein with different characteristics. As the Office is aware, evidence is of record in the parent application herein attesting to the differing nature of these proteins. For the convenience of the Office, the declarations of Sam L. Helgerson, E. G. D. Tuddenham, and Dr. Francis E. Preston are included with this response (Exhibits A, B and 12), as well as a copy of the article by Vehar, G. A., *et al., Nature* (1984) 312:337-342 (Exhibit C). This expert testimony and description in a peer reviewed journal clearly establish that nature Factor VIII and activated Factor VIII are different proteins with different characteristics. The Office might as well have cited a document describing stabilization of asparaginase or tissue plasminogen activator and asserted its relevance.

In addition, Curtis does not really describe the conditions for any freeze drying process even for activated Factor VIII.

In terms of lyophilization of activated Factor VIII, the Office cites claim 5 which is directed to an embodiment of the method of claim 1 wherein the activated Factor VIII is lyophilized after the pH of Factor VIII is adjusted in step (c). There is nothing in claim 1 that describes the addition of trehalose as a stabilizer in such lyophilization or comments on the absence of albumin. It is certainly correct that the proteins will have been removed from the preparation of activated Factor VIII by the process of claim 1, but claim 1 mentions nothing about adding trehalose.

The Office cites claim 4 as proposing stabilizing Factor VIII during the process of claim 1 using human serum albumin, sucrose and trehalose, putatively as alternatives, but this is not directed to stabilization during lyophilization (claim 5 does not depend from claim 4) but rather stabilization during the process of claim 1. Thus, the claims discussed by the Office do not make any suggestion of stabilizing Factor VIII during lyophilization using trehalose instead of albumin.

The Office then cites column 5 at lines 30-43 as assertedly teaching that activated Factor VIII can be stabilized by trehalose in the absence of albumin during lyophilization. However, this is not the case. As this paragraph reads, the stabilizers listed, which include albumin and trehalose, among others, are mentioned as stabilizing the composition "at a number of points in the process" which is, actually, the process for converting native Factor VIII into activated Factor VIII, not lyophilizing the product.

The quoted paragraph then notes that following the preparation and stabilizing, the protein can be lyophilized and stored at reduced temperatures; the nature of any stabilizing agent in the lyophilization process is just not addressed.

In short, Curtis does not teach anything at all about lyophilizing even activated Factor VIII in the presence of trehalose and the absence of albumin. The inclusion of both albumin and

trehalose on the list of possible stabilizers intended to stabilize the protein during the process of its conversion to the activated form is irrelevant to any teaching as to how the activated form is to be stabilized during lyophilization.

It should further be borne in mind that the skilled artisan reading Curtis would be well aware of the practice and perceived necessity in the art at the time the invention was made that albumin was required for stabilizing Factor VIII during lyophilization.

Applicant resubmits herewith the evidence contained in the parent application that this is the case. This evidence includes:

1. An Alpha Therapeutic Corporation advertisement in the February 15, 2000, issue of the Journal *Blood*, stating that all recombinant Factor VIII products contain albumin which is necessary for preserving the factor proteins;

2. An excerpt from the 1999 Physicians' Desk Reference describing the Helixate® recombinant Factor VIII product which is stabilized with albumin and lyophilized;

3. U.S. patent No. 4,361,509 which describes, at column 10, lines 1-3, the necessity to include human serum albumin in Factor VIII prior to storage;

4. The expert declaration of Dr. Allen Mackenzie which states that Factor VIII preparations were believed to require albumin in order to stabilize the Factor VIII;

5. A North Carolina Hemophilia Center website extract from 2002, stating that human albumin is used as a stabilizer for Factor VIII;

6. An article by Brownlee, *et al.*, stating that the purified Factor VIII is stabilized by the addition of human albumin;

7. A web-page from the Puget Sound Blood Center of November 1999, stating that recombinant Factor VIII concentrates are stabilized by adding pasteurized human serum albumin;

8. A web-page from Emory Health Sciences dated October 10, 2000, verifying that recombinant Factor VIII, at that time, was stabilized with human serum albumin;

9. A web-page from the National Hemophilia Foundation website of January 10, 2001, stating that ReFacto® is the first recombinant human Factor VIII product formulated without human serum albumin;

10. U.S. patent 6,171,825 filed 4 September 1998, indicating the desirability of ridding Factor VIII preparations from albumin;

11. WO 94/07510 stating that the use of albumin for stabilization of Factor VIII is currently used in all highly purified Factor VIII products on the market; and

12. The Declaration of Francis E. Preston which attests to the common use of albumin as a stabilizer which is undesirable but considered necessary.

Knowing that Factor VIII is routinely stabilized with albumin, the skilled reader of Curtis would never assume that trehalose is intended as a substitute for albumin as a stabilizer during lyophilization. It is as if an article on the preparation of food listing various foods, such as meat, eggs, vegetables, etc. and various methods of cooking, such as grilling, frying, roasting, baking, etc. could then be considered to teach that eggs could be grilled The skilled artisan would know that this was not possible. The skilled artisan would also know that eggs could not be fried without removing their shells, without having to be told. Similarly, the skilled artisan would understand that albumin was conventionally used as a stabilizer during lyophilization of native Factor VIII, even though its inclusion has many disadvantages, including cost, if the albumin is recombinant and

danger of contamination if it is prepared from blood. Short of an explicit statement that albumin could be excluded, the knowledgeable reader would simply assume that albumin should be present.

The importance of eliminating albumin is also emphasized by the commercial success of later-developed compositions according to the present invention which are able to dispense with this stabilizer due to the presence of trehalose. With the appearance of Advate®, a Baxter product using trehalose as stabilizer and lacking albumin, by the end of 2005, 70% of European patients using Recombinate®, a Factor VIII product which contains albumin as stabilizer, had converted to the use of Advate®; in the U.K., the conversion rate was 100%. Advate® has been approved by the Food and Drug Administration, and has generated large sales worldwide. Thus, the significance of the present invention is recognized in the marketplace.

Enclosed (Exhibit E) is a PubMed abstract of a publication in 2003 (*Drugs RD* (2003) 4:366-368) reporting that Baxter Healthcare licensed the technology claimed herein for $1,000,000 with additional milestone payments of $2,000,000, attesting to the commercial significance of this technology. Also enclosed (Exhibit F) is a review by Wang, *et al., Int. J. Pharm.* (2003) 259:1-15. Page 6 notes that "the stability of lyophilized Factor VIII products depends largely on the presence of protein stabilizers." It goes on to explain that Kogenate® and Recombinate® contain human serum albumin (HSA) and that these products are fairly stable. However, the stability of HSA-free formats called Kogenate® PS and ReFacto® is described as "significantly compromised." As noted, "an optimal formulation for lyophilized Factor VIII still needs to be explored with the goal of achieving a comparable stability that is afforded by HSA." Thus, the present invention clearly meets a long-felt need.

Thus, Curtis not only fails to teach anything about lyophilization of native Factor VIII, it also fails to teach anything about conditions for lyophilizing activated Factor VIII. There is no implication that even activated Factor VIII can be lyophilized in the presence of trehalose but in the absence of albumin.

Curtis is essential to the combination of documents on which the rejection is based. The failure of Curtis to teach what the Office asserts that it does is adequate basis to withdraw the rejection.

As to Livesey, the Office first notes that claim 17 of Livesey indicates that Livesey's process can be applied to Factor VIII. However, claim 17 depends from claim 1 which requires a suspension. A *suspension* of biological material consisting solely of Factor VIII would be impossible to obtain in view of the solubility of this protein.

Claim 1 describes a rather elaborate process which may or may not represent lyophilization. Claim 1 requires preparing a cryosolution with suspension of biological material, the cryosolution comprising a buffer, a cryoprotectant and a biological material, nebulizing it, cooling the resulting microdroplets to a temperature much lower than normal freeze-drying temperatures so that certain types of ice are formed and spraying the microdroplets against a solid cryogenic surface, continuously removing the splattered microdroplets which have become solid at this point and then drying them. It is the frozen cryosolution that is removed from the cryogenic surface and then dried (*see* column 5, lines 63, *et seq.*). Drying may be achieved by conventional freeze-drying (*i.e.* lyophilization) or by using a molecular distillation dryer (*see* column 6, lines 7, *et seq.*). Thus, claim 1 does not even necessarily describe lyophilization, and if it does, the lyophilization is from a

frozen spattered microdroplet preparation which presumably contains a cryoprotectant and buffer, not an aqueous solution.

Livesey's description of the nature of cryoprotectants begins in column 9 at line 5 and lists, among other things, trehalose, human serum albumin "and combinations thereof" (line 11). Skipping over this, the Office quotes lines 16-32 which is a discussion of "dry protectant compounds." No dry protectant compound is required in claim 1 from which claim 17 depends. (The addition of a dry protectant appears only in claim 3.) The quoted section, which begins at line 24, refers to the use of trehalose and carbohydrates to stabilize macromolecules, such as proteins and nucleic acids, when dried, as protecting the integrity of the sample. The further discussion, beginning at line 33 appears to be ignored. This discussion lists, specifically, human serum albumin plus trehalose as cryoprotectants alone or in combination with other cryoprotectants or additional components (for example, dry protectants). Reading the relevant section from column 9, lines 5-39 would not convey to the skilled artisan that trehalose alone could be used in the absence of albumin as the cryoprotectant in claim 1 from which claim 17 depends.

The Office point to the only example of Livesey that mentions trehalose, Example 5. Example 5 is concerned with stabilizing an entire virus for vaccine purposes, not a single protein. (All of the specific examples in Livesey relate to whole cells or, in the case of Example 5, an entire virus.) There are no examples of preserving individual proteins, let alone Factor VIII, which is a particularly delicate and unstable protein. This is consistent with the requirement for a suspension of biological nutrient.

In the case of a viral vaccine like the OPV of Example 5, one can probably tolerate some denaturation of proteins, and even the inactivation of some of the virus particles during processing

and storage. In the case of the labile functional protein Factor VIII, such denaturation/degradation would not be acceptable.

Also, Example 5 does not involve lyophilization or freeze-drying, but molecular distillation drying. (*See* column 23, lines 54-55), and trehalose appears to be ineffective even in this context as a stabilizer. As shown in the table reporting the results, MES buffer alone appeared to be as effective as trehalose in stabilizing the attenuated virus.

Similarly to the discussion of Curtis, the knowledge of the skilled artisan must be taken into account in how Livesey would be interpreted. Just because trehalose and Factor VIII are mentioned in the same document does not lead to the conclusion that trehalose can be used as a stabilizer for lyophilization in the absence of albumin, when the artisan already knows that albumin is required. There is nothing in the document which would contravene that understanding. Claim 1 which describes the process from which claim 17, naming Factor VIII, depends requires only a cryoprotectant. The section of Livesey quoted by the Office does not involve cryoprotectants but dry protectants. Where cryoprotectants are discussed, combinations of the listed protectants are specifically mentioned.

Example 5, as it does not relate to Factor VIII anyway, appears irrelevant on its face. Nevertheless, what it appears to show is that trehalose is no better protectant than buffer alone (*see* the table at the top of column 24).

Thus, Livesey is not germane to the present invention because it simply never addresses stabilization of Factor VIII solutions during freeze-drying.

Further, applicants find no attempt to explain why one of skill in the art would be motivated to combine Curtis with Livesey absent the teaching of the present invention, or for that matter, even

if the teachings of the present invention are considered. The present invention concerns compositions of native Factor VIII prepared by freeze drying from solution. The teachings of Curtis relate to a different protein, activated Factor VIII. The teachings of Livesey, which at least are directly concerned with processes for cryostabilization, do not concern Factor VIII as a solution, as in the present invention, but rather concern cryostabilization of suspensions of biological material. Applicants are unable to find any suggestion that would motivate one of skill in the art to combine these documents. There is no suggestion for combination in these documents themselves, they do not concern the same problem, and neither is such a high profile document that it would automatically be considered by one of skill in the art.

Double-Patenting

The pending claims were rejected as double-patenting over U.S. 6,649,386 and applications 10/658,219; 09/888,734; and 10/681,948. Terminal disclaimers are enclosed with respect to these documents.

Summary

The rejection of the pending claims depends on the combination of Lee with additional documents. Lee is cited as the sole document disclosing the claim requirement that calcium ion be present in the freeze-drying process. However, Lee's teachings are irrelevant to the amended claims. Neither Curtis nor Livesey is pertinent to the present claims for the reasons set forth above. Withdrawal of the rejection is thus proper. Passage of claims 1-3 and 6-8 to issue is therefore respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 559662000103.

Respectfully submitted,

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